REMARKS

Claims 1-6 are under consideration in this case.

Claims 1, 2, 5 and 6 have been amended following Examiner's suggestions to claim with more particularity that which the Applicants consider their invention. Support for these amendments are found throughout the specification and in the originally filed claims.

An Appendix with pending claims and with a marked-up version of the changes in the amended claims captioned "**Version with markings to show changes made**" has been attached for the Examiner's convenience. No new matter has been added by way of these amendments.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-6 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. The Examiner has given specific suggestions to amend claims 1, 2, 5, and 6, but no specific reason for rejecting claims 3 and 4. Applicants have amended claims 1, 2, 5, and 6 to rectify the problems identified by the Examiner, basically following the Examiner's suggestions. Applicants respectfully submit that amended claims 1-6 now satisfy the requirements of Section 112, second paragraph, and request that the rejections be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-6 are rejected under 35 U.S.C.§ 103(a) as being unpatentable over Guschin et al., (1997) or Khrapko et al. (U.S. Patent No. 5,552,270) or Chetverin et al. (U.S. Patent No. 5,616,478) in view of Funk et al. (U.S. Patent No. 5,973,014), and if necessary in further view of Rouchel et al., (1975) (Rouchel (1975)) and Rouchel et al., (1978) (Rouchel (1978)) and Blank et al., (1974).

As stated in the application, the present invention "involves improvement of arrays of porous polymer pads on a solid support used in biological assays." p. 3, lns. 10-11. Specifically, the improvement addresses the need for polymer pads with increased porosity so that large target molecules can easily diffuse into the pads. Consequently, binding events in the biological assays

using these polymer pads with increased porosity can occur in a truly 3-dimensional space defined by the large pores. The example disclosed in the application demonstrates that freeze-drying porous polymer pads can achieve the purpose of providing large pores allowing access of large target molecules and thereby more binding events, as compared to a standard method of preparing porous gel pads. See p. 13 (showing increased signal-to-noise ratio by using freeze-dried gel pads).

Guschin et al. teach 3-dimensional gel pads containing microchips that provide greater capacity for immobilization of probes than a 2 -dimensional glass support. Guschin et al. mention that the oligonucleotide microchips can be dried and kept for months and reused for hybridization, i.e., Guschin et al. teach drying for storage and future use. Guschin et al. do not enable the drying method. More importantly, Guschin et al. neither teach nor suggest the use of a freeze-drying method to increase the pore size within the polymer. Guschin et al. provide an improvement via the use of its 3-dimensional gel pads over the 2-dimensional glass support for microchips. This reference in no way suggests, (and therefore in no way addresses), further improvements in 3-dimensional gel pads.

Khrapko et al. provide a method for sequencing DNA and a device for carrying out said method which comprises a matrix of oligonucleotide array and gel portions. By using the gel portions, Khrapko et al. present an improvement over previous methods of DNA sequencing. See Columns 1-2. Similar to Guschin et al., this reference does not teach or suggest a need for increased pore sizes of the gel portions.

Chetverin et al. provide a method for amplification of nucleic acids in solid media. This reference does not teach or suggest the use of an array of porous polymer pads. Instead, this reference teaches the use of solid media to entrap nucleic acids to "substantially prevent a competition between different templates, since their progeny is not allowed to spread all over the reaction volume." Column 5, lines 36-39. Further, "[t]he solid matrix has a highly expanded surface that penetrates the liquid phase, so that the liquid phase gets substantially motionless," and therefore, nucleic acid templates located in different zones within the solid matrix would not

cross-contaminate each other. Column 6, lines 55-57. Thus, this reference does not teach or suggest a need for increased pore sizes in the gel matrix to allow more access of target molecules. In fact, it teaches away from such an enhanced-access porous polymer pads, because the more free-diffusion the target molecules, the more likely cross-contamination between nucleic acids located in different zones of the solid matrix would occur. A reference which leads away from the claimed invention cannot render the invention obvious.

Funk et al. provide a process for the preparation of porous, hydrophilic, highly swellable hydrogels which are used as products absorbing aqueous solutions in the production of hygiene articles. This reference teaches a freeze-drying process to prepare porous, hydrophilic, and highly swellable polymers by freezing the polymers at -10°C – -20°C instead of liquid nitrogen temperature as taught by the present invention. The Examiner characterizes Funk et al. as "using the amount of water in the swollen polymer freeze dried to obtain a desired pore size." Nevertheless, the desired pore size in Funk et al. is to maximize absorption of aqueous solutions by hygiene products. Further, Funk et al. neither teach nor suggest the use of the highly swellable hydrogels in an array of polymer gels pads for biological assays. Thus, this reference does not teach or suggest that the increased pore size would allow macromolecules, (e.g., targets in bioassays), to access the 3-dimensional polymer gel matrix.

Blank et al. and Rouchel (1975) teach freeze-drying of polyacrylamide gels under conditions that prevent the gel matrix from shrinking during dehydration and provide scanning electron micrographs of the dehydrated gel showing a sponge-like structure. Freeze-drying in these two references is a necessary step of sample preparation for scanning electron microscopy ("SEM"). Neither of these references teaches or suggests that freeze-drying of the gels would increase the porosity of the polymers, as they could only observe freeze-dried samples with SEM. Rouchel (1978) teaches the technique of freeze-etching a slab gel and observing the pore size of the gels by Transmission Electron Microscopy (TEM). Again, freeze-etching is a necessary step of sample preparation (to preserve sample structure) for TEM. Similar to Blak et

al. and Rouchel (1975), Rouchel (1978) provides no teaching or suggestion that freeze-drying may increase the porosity of the slab gel observed by TEM in this study.

As the Examiner is aware, a *prima facie* case of obviousness requires some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See MPEP § 2142.

The Examiner states that it "would have been obvious to carry out the drying of the array of polymer gel pads on the support of Guschin et al or Khrapko et al or Chetverin et al by freeze drying to obtain to the function of freeze drying to produce a porous, highly swellable polymer of a desired pore size and distribution as disclosed by Funk et al."

While the Examiner has noted components of each reference, Applicants respectfully submit that none of the prior art references provides any teaching or suggestion to motivate one of skill in the art to combine the above references, resulting in the current invention. Applicants respectfully remind the Examiner that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills,* 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01. The motivation to combine the references to obtain an array of polymer gel pads of desired pore size is legally incorrect under MPEP §§ 2143 and 2144.03, without the references themselves providing the desirability of the combination.

As discussed above, both Guschin et al. and Khrapko et al. provide an improvement over their respective previous methods by using polymer gel pads. Neither of these references teaches or suggests that large molecules may not fully access the 3-dimensional gel matrix, and therefore, neither teaches or suggests the desirability of further increasing the porosity of the polymer gels. Therefore, one of skill in the art would not be motivated to combine either of these references with Funk et al. to obtain an array of polymer gel pads of increased porosity by a freeze-drying method for biological assays.

Further, Chetverin et al. seem to teach away from increasing the porosity of the solid matrix, as the purpose of solid matrix in this reference is to separate and thereby avoid cross-

contamination of nucleic acids located in different zones of the solid matrix. While Blank et al., Rouchel (1975), and Rouchel (1978) present structural observations of polymer gel matrix, none of these references teaches or suggests increased porosity of the polymer gel matrix by their respective sample preparation procedure, i.e, freeze-drying or freeze-etching. Therefore, none of these references would motivate one of skill in the art to combine Funk et al. to obtain an array of polymer gel pads of increased porosity by a freeze-drying method for biological assays.

Finally, although Funk et al. teach a method of freeze-drying water-swollen polymer gels to obtain desired pore size, this reference in itself does not teach or suggest the combination of its highly swellable hydrogels with arrays used in biological assays.

Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established, absent evidence of explicit motivation to combine references. Therefore, claims 1-6 are not obvious over Guschin et al. or Khrapko et al. or Chetverin et al. in view of Funk et al., and in further view of Rouchel(1975) and Rouchel Rouchel (1978) and Blank under § 103(a), and Applicants respectfully request withdrawal of the rejection.

For all the foregoing reasons, Applicants submit that Claims 1-6 are patentable and respectfully request allowance of the pending claims. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
FLEHR HOHBACH TEST
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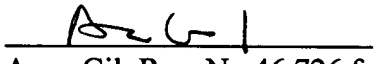
Dated: February 28, 2002



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APPENDIX OF PENDING CLAIMS

We claim:

1. (Amended) In a method of providing an array of porous polymer pads on a solid support and then drying the array of porous polymer pads on said solid support, the improvement comprising carrying out said drying by freeze-drying by a method comprising:
   a. freezing said array of porous polymer pads on said solid support, and
   b. drying said array of porous polymer pads on said solid support at reduced pressure,
   wherein said freeze-drying increases the pore size of the porous polymer.

2. (Amended) An array of porous polymer pads on a solid support, wherein said porous polymer pads are freeze dried by:
   a. providing an array of porous polymer pads on a solid support,
   b. freezing said array on said solid support, and
   c. drying said array on said solid support at reduced pressure,
   thereby increasing pore size in the porous polymer.

3. The array of claim 2 wherein a specific binding substance is covalently linked to said porous polymer pads.

4. The array of claim 3 wherein the specific binding substance is a polynucleotide.

5. A method for freeze drying an array comprising porous polymer pads on a solid support, said method comprising:
   a. freezing said array on said solid support, and
   b. drying said array on said solid support at reduced pressure.

6. The method of claim 5 wherein the porous polymer pads are frozen at liquid nitrogen temperatures and dried under vacuum to remove water by sublimation.

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"**Version with markings to show changes made**"

1. (Amended) In a method of providing ~~for improving~~ an array of porous polymer pads on a solid support and then drying the array of porous polymer pads on said solid support ~~surface~~, ~~said~~ the improvement comprising carrying out said drying by freeze-drying by a method comprising:
   a. freezing said array of porous polymer pads on said solid support, and
   b. drying said array of porous polymer pads on said solid support at reduced pressure,
   wherein said freeze-drying ~~improvement~~ increases the pore size of the porous polymer pads.

2. (Amended) An array of porous polymer pads on a solid support, wherein said porous polymer pads are freeze dried by ~~comprising~~:
   ~~porous polymer pads on a solid surface, wherein the porous polymer pads are freeze-dried by~~:
   a. providing an array of porous polymer pads on a solid support,
   b. freezing said array on said solid support, and
   ~~b~~c. drying said array on said solid support at reduced pressure,
   thereby increasing pore size in the porous polymer pads.

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